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HOFFMANN-LA ROCHE INC.
PATENT LAW DEPARTMENT
340 KINGSLAND STREET
NUTLEY, NJ 07110

EXAMINER	
DANG, IAN D	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/815,449	GRAUS ET AL.	
	Examiner	Art Unit	
	Ian Dang	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *12-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☒ Claim(s) *4 and 5* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-11 in the communication filed on 110/31/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 12-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b).

Claims 1-11 are pending and under examination.

Claim Objections

Claims 4 and 5 objected to because of the following informalities: "IFG-IR" is misspelled and should read IGF-IR. Appropriate correction is required.

Claim Rejections - 35 USC § 112 (Biological Deposit Rule)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is not clear from the disclosure that deposits of the hybridoma cell lines HuMab Clone 1A, HuMab Clone 23, and HuMab Clone 8 meet all the criteria set forth in MPEP 608/01 (p)(C),

items 1-3. Assurance of compliance may be in the form of a declaration or averment under oath. A suggested format for such a declaration or averment is outlined below:

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL

A declaration by applicant, assignee, or applicants agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection and rejection based on a lack of availability of biological material.

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address.

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material will be irrevocably removed upon the granting of a patent.

5. States that the material has been deposited under conditions that ensure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 35 CFR 1.14 and 35 USC 122.

6. States that the deposited material will be stored with all care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case at least thirty (30) years after the date of a deposit or for the enforceable life of the patent, whichever is longer.

7. Acknowledges the duty to replace the deposit should the depository be unable to furnish a sample when requested due to the condition of the deposit.

8. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by

fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, name and address of the depository, and the complete taxonomic description.

As a possible means of completing the record, applicants may submit a copy of the deposit receipt.

Claim Rejections - 35 USC § 112 (Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody molecule comprising termed "1A" comprising the amino acid sequences set forth as SEQ ID Nos 1 and 2 does not reasonably provide enablement for the claimed substitutions or deletions in the antibody heavy and light chains. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Claims 1- 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering the monoclonal antibody 1A cells *in vitro*, does not reasonably provide enablement for a pharmaceutical composition comprising the antibody. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include: (1) Nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the breath of the claims, (7) the quantity of experimentation needed, (8) relative skill of those in the art.

Nature of the invention and breath of the claims

The claims are drawn to an antibody which binds to IGF-IR wherein the antibody inhibits the binding of IGF-I and IGF-II to IGF-IR, induces cell death in cellular toxicity assay, several substitutions or deletions in the IGF-IR antibody heavy and light chains, and a pharmaceutical composition comprising the antibody. The invention is broad because the recitation of claims 1 and 6-9 encompasses numerous antibodies with different CDRs composing the light and heavy chain of the antibody and claim 11 encompasses *in vivo* therapy for treating a large number of diseases.

Unpredictability and state of the art

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is

expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

In addition, Colman (Research in immunology 145:33-36, 1994) teach that example of antigen-antibody interactions paints a confusing picture and a conservative substitution may abolish binding (see page 35). Thus, it is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions or contain conservative substitutions, have the required binding function.

Moreover, the state of the art for IGF-IR is well characterized *in vitro*, such as in assays inhibiting cellular growth, but an antibody IGF-IR as a therapeutic is not established. The claims encompass the experimental and unpredictable field of *in vivo* therapy for cancer. Those of skill in the art recognize that, although *in vitro* assays are generally useful to screen the effects of agents on target cells, clinical correlation with treatment of a disease *in vivo* does not necessarily follow. The greatly increased complexity of *in vivo* therapy compared to the narrowly defined and controlled conditions of an *in vitro* assay does not permit a direct extrapolation of *in vitro* assay results to mammal or human therapy with any degree of predictibility. *In vitro* assays cannot adequately assess cell to cell interactions which may be important in a particular pathological state. Furthermore, a therapeutic agent must accomplish

several tasks to be effective; it must be delivered into circulation, it must interact at the proper site at a therapeutic concentration, and it must remain effective for a sufficient period of time. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In an *in vitro* assay, the agent is in direct contact with target cells during the entire exposure period, whereas in *in vivo* therapy, exposure at the target site may be delayed and/or reduced. The composition may be inactivated *in vivo*, such as by proteolytic degradation or immunological inactivation, before producing the desired effect. See Jain et al., Cancer and Metatasis Review, vol. 9, pp. 253-266 and Dermer, Biotechnology 12:320, 1994, for a discussion of the differences between *in vitro* assay and *in vivo* therapy and the numerous pitfalls associated with *in vivo* cancer therapy

In view of these teachings with respect to amino acid substitutions and deletions in the heavy and light chain of the antibody and the therapeutic use of the IGF-IR antibody, any amino acid changes in the sequence encoded an IGF-IR antibody and the pharmaceutical composition comprising the IGF-I IR antibody or are not predictable.

The amount of direction or guidance present

Applicants' disclosure is limited to the characterization of the IGF-IR antibody 1A encoded with SEQ ID NO:1 and SEQ ID NO:2 (page 35) in several *in vitro* assays (Examples 1-11 and 13-15) and administering it to nude mice injected with tumor cells (Example 12). The specification does not provide guidance whether the IGF-IR antibody 8 and the IGF-IR antibody 23 have the same functional and structural characteristics as the ones for IGF-IR antibody 1A. [Similarly, Applicants have provided support for the hybridoma cell line HuMab clone 1A but not for the HuMab Clone 23 nor for the HuMab Clone 8

In addition, the specification does not provide guidance or direction regarding how the IGF-IR antibody 1A can retain its activities by substituting or deleting amino acid residues in the

CH1, CH2, CH3, hinge domains, and/or the framework domain with the corresponding human sequence while maintaining all of the CDRs of the heavy chain, the light chain or both the heavy and light chains.

Working Examples

Although Applicants have provided a numerous examples for the IGF-IR antibody 1A encoded by SEQ ID NO:1 and NO:2 (Examples 1-15) and administering IGF-IR to nude mice injected with tumor cells, the specification does not provide any examples for an antibody 1A with substitutions or deletions in the antibody heavy and light chains. In addition, the specification does not provide any examples regarding the pharmaceutical composition in a diesease and *in vitro* activities with the IGF-IR antibody 8 or the IGF-IR antibody 23.

The quantity of experimentation needed

Because the claims are broadly drawn to an IgG1 antibody which binds to IGF-IR, inhibits the binding of IGF-I and IGF-II to IGF-IR, and induces cell death in cellular toxicity assay and a pharmaceutical composition comprising the antibody, and because Applicant's disclosure does not contain sufficient teachings to overcome the unpredictability taught in the art, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In Claim 1 Applicants recites a ratio of inhibition of the binding of IGF-I and IGF II to IGF-IR of 1:3 to 3:1 but the claim does not teach the method for obtaining the ratio of inhibition. The claim is incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination.

The metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The claims are drawn to an IgG1 isotype antibody that binds to IGF-IR, which inhibits the binding of IGF-I and IGF-II, inhibits of the binding of IGF-I and IGF-II to IGF-IR, and induces cell death of a preparation of IGF-IR expressing cells in an antibody dependent cellular toxicity assay or in a complement dependent cytotoxicity (CDC) assay. The antibody is a human or

humanized and binds IGF-IR with an affinity of about 10^{-11} to 10^{-8} M (K_D) and of about 10^{-11} to 10^{-9} M (K_D).

The antibody further comprises complementary determining regions (CDRs) having the following sequences with an antibody heavy chain having CDRs comprising CDR1 (aa 31-35), CR2 (aa 50-66) and CDR3 (aa 98-108) of SEQ ID NO:1 wherein amino acid 31 can be asparagines (Asp) or serine (Ser), amino acid 66 can be glycine or can be deleted, and amino acid 104 can be glutamic acid or aspartic acid. Moreover, the antibody light chain having CDRs comprising CDR1 (aa 18-34 or aa 24-34), CDR2 (aa 50-56) and CDR3 (aa 89-98) of SEQ ID NO:2, wherein the amino acid 96 can be praline or isoleucine, and amino acid 98 can be phenylalanince or can be deleted.

Furthermore, the antibody comprises a heavy chain comprising a variable region (VH) of SEQ ID NO:1 wherein amino acid (aa) is serine or arginine, aa 31 is asparagines or serine, aa 94 is histidine or tyrosine, and aa 104 is aspartic acid or glutamic acid further comprising a human heavy chain constant region (CH). A light chain comprising a variable region (VL) of SEQ ID NO:2 wherein aa 96 is praline or isoleucine, aa 100 is praline or glutamine, aa 103 is arginine or lysine, aa 104 is valine or leucine and aa 105 is aspartic acid or glutamic acid and further comprising a human light chain constant region (CL).

The claimed invention is further drawn to an antibody obtainable from a hybridoma cell line HuMab clone 1A, huMab clone 23, and huMab clone 8 and a pharmaceutical composition comprising the antibody of claim 1.

Claims 1, and 3-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Li et al (2000, cited in the IDS).

Li et al. teach antibody that binds to IGF-IR and inhibits the binding of IGF-I and IGF-II to IGF-IR (page 247 column 1, 2nd paragraph) and is a IgG1 isotype (page 243, Abstract) matching

the limitations of claim 1. In addition, Li et al. teach that the antibody αIGF-IR scFv is a human or humanized antibody meeting the limitations of claim 3 (page 244, column 1, 2nd paragraph). Moreover, the antibody binding constants determined by BIOCORE were $1x10^{-9}$ M and $1x10^{-8}$ M (K_D) meeting the limitations of claims 4 and 5 (page 247, column 1, first paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 6 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. (2000 cited in the IDS) as applied to claims 1 and 3-5 above in view of Bruggemann et al. (1987 cited in the IDS) and Cohen et al. (US Patent 7,037,498 filed of January 4, 2002, given the priority of January 5, 2001).

Li et al. teach an IgG1 isotype antibody that binds to IGF-IR, which inhibits the binding of IGF-I and IGF-II, inhibits of the binding of IGF-I and IGF-II to IGF-IR, and induces cell death of a preparation of IGF-IR expressing cells in an antibody dependent cellular toxicity assay or in a complement dependent cytotoxicity (CDC) assay. The antibody is a human or humanized and binds IGF-IR with an affinity of about 10^{-11} to 10^{-8} M (K_D) and of about 10^{-11} to 10^{-9} M (K_D).

Li et al. do not teach an IgG1 isotype antibody that induces cell death of a preparation of IGF-IR expressing cells in an antibody dependent cellular toxicity assay or in a complement dependent cytotoxicity (CDC) assay, an antibody with the light chain encoded by SEQ ID NO2, an antibody with the heavy chain encoded by SEQ ID NO:1 and, and a pharmaceutical composition comprising the claimed antibody.

Bruggeman et al. teach an IgG1 isotype antibody that induces cell death of a preparation of IGF-IR expressing cells in an antibody dependent cellular toxicity and in a complement dependent cytotoxicity assay (page 1358, Figure 6). The goal of these assays is to determine the *in vitro* antigenic specificities of the chimeric antibodies, such as for the antibody binding to IGF-IR.

Cohen et al. teach an IGF-IR antibody comprising a heavy chain with the amino acid sequence NO:6, which has 100% identity with SEQ ID NO:2 of this instant application, and light chain encoded by the amino acid SEQ ID NO:16, which has 100% identity with SEQ ID NO:2 of the instant application (column 16, lines 28-38).

It would have been obvious prima facie obvious for one of ordinary skill in the art at the time of the invention was made to use the antibody dependent cellular toxicity and complement toxicity assays taught by Bruggemen et al. and the IGF-IR antibody taught by Cohen et al. for an IgG1 isotype antibody that binds to IGF-IR, which inhibits the binding of IGF-I and IGF-II, inhibits of the binding of IGF-I and IGF-II to IGF-IR, induces cell death of a preparation of IGF-IR expressing cells in an antibody dependent cellular toxicity assay or in a complement dependent cytotoxicity (CDC) assay, an antibody with the light chain encoded by SEQ ID NO2, an antibody with the heavy chain encoded by SEQ ID NO:1. One of ordinary skill in the art at the time the invention was made would have been motivated to do so because it would provide valuable information regarding to the comparisons in the abilities of the different IgG subclasses to mediate a variety of effector functions. Accordingly, the invention taken as a whole is prima facie obvious.

Conclusion

No claims are allowed.

Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ian Dang whose telephone number is (571) 272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ian Dang
Patent Examiner
Art Unit 1647
November 27, 2006

Brenda Brumback
BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600